# Optimising the management of allergic rhinitis: an Australian perspective

Ronald S Walls, Robert J Heddle, Mimi LK Tang, Ben J Basger, Graham O Solley and Guan T Yeo

lthough often perceived as trivial or "inconvenient", allergic rhinitis (AR) is a major chronic respiratory disease by virtue of its high prevalence and significant effect on quality of life, work or school performance, and productivity.<sup>1</sup>

The prevalence of all allergic diseases, including AR, has increased dramatically over the past few decades, particularly in developed countries. One study of self-reported asthma and hayfever in Tasmanian adults revealed the lifetime prevalence of hayfever among adults had doubled from 19.2% in 1968 to 41.3% in 1991–1993.

Data collected in general practice suggest the national point prevalence of AR is 18.7%, with the highest prevalence among the 25–44-years age group (24.4%).<sup>3</sup> Children also feature as sufferers, with the prevalence of current AR at 12% in 6–7-year-olds and 19.6% in 13–14-year-olds.<sup>4</sup>

For people with AR, quality of life can be considerably reduced, leading to impaired performance of daily activities, cognitive function and classroom productivity, and reduced psychosocial wellbeing. AR also creates a significant economic burden: the Australian Institute of Health and Welfare estimated that, in 1994, respiratory disease (including AR) accounted for 8.0% of total healthcare system costs. 6

Poorly controlled AR may be associated with various complications and comorbid conditions. AR and asthma frequently coexist, and AR usually precedes and is a significant risk factor for asthma. <sup>1,7-9</sup> Furthermore, evidence shows that treating AR, particularly with intranasal corticosteroids (INCS), can reduce asthmarelated emergency department visits and hospitalisations. <sup>10</sup> Other conditions that are associated with AR include sinusitis, <sup>11</sup> otitis media <sup>1,11</sup> and nasal polyposis. <sup>1</sup>

There have been various international developments in the approach to managing AR. In addition, recent changes to the scheduling of drugs used in treating allergic disease in Australia

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#### **ABSTRACT**

- Allergic rhinitis (AR) is one of the most prevalent medical conditions. It has significant effects on quality of life and can have considerable socioeconomic effects.
- The traditional classification of perennial and seasonal rhinitis
  does not distinguish between provoking factors, nor does it
  indicate the most appropriate treatment. A more useful
  classification is based on symptoms, which may be
  intermittent or persistent, and vary widely in severity.
- The goal of management is to achieve optimal symptom control. Therapeutic options include allergen avoidance, pharmacotherapy and immunotherapy.
- Antihistamines and intranasal corticosteroids (INCS) have become the cornerstones of therapy. A variety of effective treatments are available for consumers to self-select, without the advice of a doctor or pharmacist.
- INCS are widely recognised as the most effective pharmacotherapy for AR, in both adults and children. The efficacy of various preparations is similar, but those with low systemic bioavailability are preferred for children and for patients who are also receiving inhaled, topical or systemic corticosteroids.

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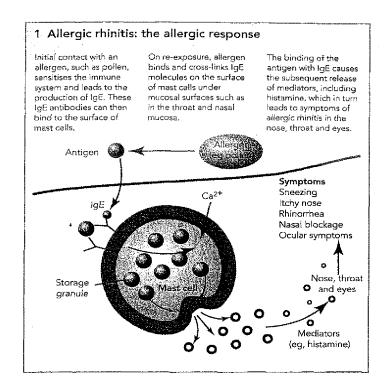
have important repercussions for the management of this disease and, potentially, for the risk of complications. This article is intended to highlight these changes and address the changing treatment environment for AR in Australia.

# Definition and diagnosis

AR is a symptomatic disorder of the nose induced by inflammation mediated by immunoglobulin E (IgE) in the membrane lining the nose after allergen exposure. Allergic individuals become sensitised to and may develop IgE antibodies against allergens such as pollen, dust mites, animal dander and mould spores. Antigenspecific IgE binds to high-affinity receptors on tissue mast cells. On further exposure to the specific allergen, antigen binds to IgE antibodies on the mast cells and mast-cell degranulation occurs, leading to release of chemical mediators (Box 1). 12

This immediate allergic response to antigen is termed the early-phase response. The mediators released during this phase include histamine, kinins, neutral proteases, cytokines (such as tumour necrosis factor  $\alpha$ ) and a variety of interleukins. <sup>12</sup> Activation of mast cells also leads to the production of leukotrienes and prostaglandins from arachidonic acid. Together, these mediators result in the characteristic symptoms of AR — watery rhinorrhoea, sneezing and itching — within minutes of allergen exposure. <sup>12</sup>

This is followed several hours later by the late-phase response, involving the infiltration of inflammatory cells and the release of mediators into the nasal mucosa. The symptoms are essentially the same as in the early-phase response, but congestion predominates.



Diagnosis of AR requires a detailed and accurate history, physical examination, and allergy investigation to assist in characterising the patient and identifying the provoking factors. Dobtaining a general medical history should be followed by questions on personal and family history of allergic conditions, including eczema, asthma and AR, as well as details of the patient's environment and occupation. It is important to be mindful that, although the classical symptoms of itching, irritative nose, rhinorrhoea and eye symptoms particularly favour a diagnosis of AR, they are not specific, and may be the result of a viral infection or vasomotor rhinitis. Conversely, their absence does not exclude AR, as blockage may be the predominant symptom in persistent AR. The physical examination should focus on the nose, throat, eyes, ears and, when appropriate, lung function.

Allergy testing should be undertaken to determine the presence of allergen-specific IgE. This can be done by skin-prick testing or radioallergosorbent test. Allergens are selected according to probability based on clinical history. Positive test results should be coupled with clinical features consistent with AR to affirm diagnosis. For more detail on the diagnostic process, readers are referred to a recent article by Puy. 13

#### Classification

The original classification of AR was based on the timing of allergen exposure — seasonal or perennial. A newer system, proposed in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines in 2001, classifies AR according to the timing of symptom presentation — intermittent or persistent (Box 2).

The ARIA system is more appropriate for use in Australia for several reasons:

• With the traditional system, "perennial" refers to AR caused by indoor allergens such as dust mites, moulds, insects and animal dander, whereas "seasonal" allergy is related to outdoor allergens

# 2 ARIA guidelines for classification of allergic rhinitis1

#### Timing of symptoms

Intermittent

Symptoms present for:

- less than 4 days per week, or
- · less than 4 weeks at a time

Persistent

Symptoms present for:

- · more than 4 days per week, and
- more than 4 weeks at a time

#### Severity and quality of life

Mild

- no impairment of sleep, daily activities, leisure or sport, school or work.
- no troublesome symptoms

Moderate to severe One or more of the following are present:

- · impairment of sleep
- impairment of daily activities, leisure or sport
- impairment of school or work
- troublesome symptoms

ARIA = Allergic Rhinitis and its Impact on Asthma. Adapted with permission from Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; 108: S147-S334. Copyright 2001, American Academy of Allergy, Asthma and Immunology.

such as pollens and moulds. However, in certain regions of Australia, pollens and moulds may be perennial allergens.

- Even patients allergic to "seasonal" allergens may have symptoms for much of the year. For example, in certain regions of Australia, particularly Queensland, it can be very difficult to define the pollen season.
- Most patients are sensitised to multiple allergens many patients allergic to pollen are also allergic to moulds — meaning that symptoms may be present throughout the year.<sup>1</sup>

#### Management options

The goal of management is to achieve optimal symptom control. Achieving this goal depends on what triggers the condition, what the symptoms are, and symptom severity.

# Allergen avoidance

The first approach that should be considered is minimising exposure to environmental trigger factors. This approach is relatively harmless. <sup>14</sup> Although two meta-analyses of trials of allergen avoidance through reduction of house dust mite antigen proved inconclusive, <sup>14,15</sup> authors of both reviews called for further adequately powered trials to optimise clinical practice. Avoidance measures are biologically plausible, and many practitioners view them as valuable. Encouragingly for AR patients, the nose may be more responsive to avoidance measures than the lower airways. <sup>16</sup>

#### Pharmacotherapy

# Managing AR in adults

With a range of over-the-counter (OTC) treatments for AR available (Box 3), most Australian adults now self-medicate for AR. A 2002 survey of hayfever and allergy sufferers revealed that nearly two-thirds of respondents did not consult their doctor about their

# 3 Treatment options for allergic rhinitis in adults and children aged 12 years or older (as at August 2004)

Schedule 2 (Pharmacy Medicine)

Intranasal corticosteroids

2 sprays into each nostril, twice daily (maintenance: 1 spray into each nostril, once daily) Beclomethasone dipropionate 50 µg/spray

4 sprays into each nostril, once daily, morning, or 2 sprays into each nostril twice daily (maintenance: Budesonide 32 µg/spray

2 sprays into each nostril once daily, morning, or 1 spray into each nostril twice daily)

Fluticasone propionate 50 µg/spray

2 sprays into each nostril, once daily, morning (maintenance: 1 spray into each nostril, once daily)

Antihistamines (see also Box 4)

1 spray into each nostril, twice daily Azelastine hydrochloride 0.14 mL/spray

Cetirizine HCl 10 mg/tablet (for use in adults) 1-2 tablets once daily

Fexofenadine HCl 60, 120, or 180 mg/tablet 1 tablet (60 mg), twice daily or 1 tablet (120 or 180 mg) once daily

Fexofenadine HCI 60 mg +

1 tablet every 12 hours

pseudoephedrine HCl 120mg/tablet

1 tablet, once daily Loratadine 10 mg/tablet

Loratadine 10 mg + pseudoephedrine

1 tablet, once daily

sulfate 240 mg/tablet

2 sprays in each nostril, twice daily Levocabastine HCl 0.5 mg/ml

Intranasal decongestants

Oxymetazoline HCl 500 µg/ml 1-3 sprays in each nostril, twice daily 1 spray in each nostril, up to 4 times daily Xylometazoline HCl 0.1 mg/ml

Oral decongestants

Phenylephrine HCl 5 mg/5 ml 10 mL every 4 hours

Intranasal mast-cell stabilisers

1 spray into each nostril 4 times daily Sodium cromoglycate 2.6 mg/spray

Intranasal anticholinergics

2-4 sprays (21 µg) into each nostril 2-3 times daily, or 1-2 sprays (42 µg) 2-3 times daily Ipratropium bromide 21 or 42 µg/15 mL

Schedule 3 (Pharmacist Only Medicine)

Antihistamines (See Box 4)

Oral decongestants

Pseudoephedrine HCl 60 mg/tablet

1 tablet 3-4 times daily

Schedule 4 (Prescription Only Medicine)

Intranasal corticosteroids

2 sprays in each nostril, once daily (morning) or 1 spray in each nostril twice daily (maintenance: Budesonide 64 µg/spray

1 spray in each nostril, once daily)

2 sprays in each nostril, once daily (maintenance: 1 spray in each nostril, once daily) Mometasone furoate 50 µg/spray

current AR treatment (Newspoll Omnibus. Data on file, Glaxo-SmithKline). The current options for self-medication include antihistamines, INCS and decongestants.

Of these options, INCS are the most effective and are considered first-line therapy for persistent AR and for moderate to severe intermittent AR in adults. 1,17-20 In systematic reviews and metaanalyses, INCS have been shown to be superior to antihistamines in controlling nasal symptoms of AR. 19-21 Moreover, INCS are more cost-effective than oral antihistamines. 19

INCS are well tolerated and can be used long term without atrophy of the nasal mucosa. 1,17 Most side effects are due to local irritation. Studies in adults suggest minimal side effects with use of nasal steroids in recommended doses. Furthermore, studies of new steroid preparations, even in relatively high doses, reveal no systemic steroid effect on the hypothalamic-pituitary-adrenal axis, as assessed by morning cortisol concentrations, cosyntropin stimulation and 24-hour urinary free cortisol excretion. 18

There is no clear evidence that one preparation is more effective than another.<sup>22</sup> The two areas in which a difference exists are in systemic bioavailability and cost. Bioavailability is the percentage of the drug systemically available for pharmacological action after topical administration. It reflects absorption across the nasal mucosa (greater for water-soluble drugs such as budesonide), absorption of swallowed drug, and the degree to which the drug is inactivated by first-pass metabolism in the liver.23

We suggest that, for adults who are not receiving other corticosteroids, the choice of INCS can be guided by personal preference, cost and accessibility. For children and all patients who are also receiving inhaled, topical or systemic preparations, a drug with low bioavailability (fluticasone propionate, mometasone furoate) should

be chosen, and dose of INCS taken into account in assessing total corticosteroid administered.

Older antihistamines are still available and are used extensively in combination with oral decongestants for cold and flu remedies (Box 4). These earlier antihistamines commonly cause central nervous system (CNS) effects such as somnolence, sedation, drowsiness, fatigue, loss of attention and impaired psychomotor performance, as well as anticholinergic effects, including difficulty in micturition, impotence, constipation and other gastrointestinal symptoms. <sup>24</sup> Because of the sedative effects, these drugs are contraindicated in patients who undertake activities such as driving. They are not the drugs of choice in children. The second-generation antihistamines have a more favourable side-effect profile.

Other effective therapies also need to be used with care. In cases of severe nasal blockage, intranasal decongestants can be used for 2–3 days to improve access to the nasal mucosa for INCS, but overuse of these can result in rhinitis medicamentosa.

Oral decongestants are helpful in specific cases (for example, if a patient needs to travel by plane). However, their use is contraindicated in some groups, including people with hypertension or coronary artery disease, and they should be used with caution in patients with heart disease, hyperthyroidism, elevated intraocular pressure, prostatic

enlargement or bladder dysfunction. Common adverse effects involve CNS stimulation and include nervousness, excitability and insomnia.  $^{25}$ 

Anti-allergy eye drops are an effective adjunctive therapy when ocular symptoms persist despite treatment (Box 5). Mast-cell stabilisers and cromones are safe for medium- or long-term use, but require regular and frequent use for optimal results.

For patients whose symptoms are not adequately controlled by OTC therapies, prescription treatments are available, including certain INCS. Systemic steroids should only be used in exceptional circumstances in adults on a short-term basis.

New treatment options, such as leukotriene-receptor antagonists (eg, montelukast), are being evaluated for use in managing AR.

However, the results to date suggest they are not more efficacious than INCS. 26

# Selection of pharmacotherapy

Adherence to an evidence-based protocol for the treatment of seasonal AR, such as the one presented in this article, produces better outcomes for patients than unstructured application of various treatment modalities.<sup>27</sup> Box 6 outlines the key decision-making steps in determining optimal pharmacotherapy for adults with AR.

# Considerations for managing AR in children

The diagnosis and treatment of AR in children follows essentially the same process as in adults. However, selection of therapy in children requires careful consideration to balance the pros and cons of the treatment options (Box 7).

# 4 Over-the-counter firstgeneration antihistamines

#### Schedule 2

Brompheniramine maleate + phenylephrine HCl

Brompheniramine maleate + dextromethorphan hydrobromide + phenylephrine HCI

Chlorpheniramine maleate + paracetamol + pseudoephedrine HCl

Chlorpheniramine maleate + phenylephrine HCI

Diphenhydramine HCl + ammonium chloride + sodium citrate

Triprolidine HCl + pseudoephedrine HCl

Triprofidine HCl + paracetamol + pseudoephedrine HCl

Schedule 3

Azatadine maleate

Cyproheptadine HCI

Dexchlorpheniramine maleate

Diphenhydramine HCI+

phenylephrine HCl

Methdilazine HCl

Pheniramine maleate

Promethazine HCl

INCS are now the drugs of choice in children with AR. 28 Concerns that INCS may cause systemic side effects, such as suppression of growth and bone metabolism, have been allayed.<sup>23</sup> One study showed that fluticasone has no clinically significant effect on lower-leg growth velocity in children aged 4-11 years.30 Mometasone use shows no evidence of growth suppression in children aged 3-9 years, 31 and a recent trial of budesonide in children aged 5-15 years revealed no negative effects on growth,32 Local side effects of INCS are also minimal. After 3 months' use of fluticasone in children aged 3-11 years, rhinoscopy showed no evidence of thinning of the nasal tissues or atrophy of the nasal mucosa.<sup>33</sup>

Second-generation antihistamines are useful when mild or intermittent symptoms are present. Older compounds, such as chlorpheniramine and diphenhydramine, should be avoided, as they can cause CNS dysfunction, impair cognition and increase somnolence, thereby exacerbating the effects of AR on children's learning. 34,35

Although some drugs (eg, loratadine) are indicated for children from 1 year of age, children younger than 2 years should be referred to an allergist/immunologist for

diagnosis and subsequent management.

#### Rescheduling of INCS and the AR healthcare team

The rescheduling to Schedule 2 of beclomethasone in 2003 and budesonide, mometasone and fluticasone in 2004 gives patients access to a wider range of effective treatments. With these changes in scheduling comes a shift in the burden of care. The pharmacy will become the focal point for initiation of treatment for many patients. Educational programs are essential to ensure that pharmacists and their assistants are appropriately equipped to counsel patients with allergic disease.

However, there is a continued need for a team approach. When

faced with a patient whose condition is unresponsive to OTC treatments, it is important for pharmacists to advise patients to speak to their general practitioner (Box 8). Similarly, GPs can be confident that referral for specialist review of patients with seemingly intractable, chronic or complex disease will provide access to effective alternative treatment options, such as immunotherapy.

# Immunotherapy (desensitisation)

The beneficial effects of allergen-specific immunotherapy on symptoms and quality of life in patients with AR are now widely accepted. <sup>18</sup> Patients with AR should be considered candidates for immunotherapy based

# 5 Ocular treatments

Ocular lubricants

Various

Antihistamines

Anatazoline

Levocabastine

Antihistamines with vasoconstrictors

Naphazoline HCl + pheniramine maleate

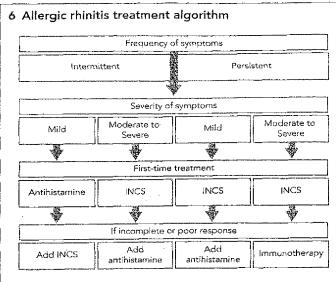
Mast-cell stabilisers

lodoxamide trometarol

Olopatadine HCl

Cromones

Sodium cromoglycate



In all patients consider:

- Intransal saline to counteract drying from using INCS, also has mucus-diluting properties.
- Anti-allergy eyedrops if allergic conjunctivitis persists despite treatment.
- Ipratropium bromide effective in cases of intractable rhinorrhoea.

#### Avoid:

- Intranasal decongestants except in short term use.
- Oral decongestants where contraindicated (eg, hypertension, coronary artery disease).

INCS - Intranasal corticosteroids

# 7 Pros and cons of pharmacotherapeutic options for allergic rhinitis in children

Pros

#### Cons

#### Antihistamines

- Useful where mild/ intermittent symptoms are present<sup>28</sup>
- Intranasal corticosteroids
- Useful in children with moderate to severe symptoms and persistent symptoms; superior to antihistamines<sup>28,29</sup>
- Newer compounds such as fluticasone propionate and mometasone furoate have low systemic bioavailability (<1%)<sup>23</sup>
- Decongestants
- Provide temporary relief of nasal congestion

- Not as effective if congestion is present
- Older drugs have sedative and gastrointestinal effects
- Must consider total steroid load for children who take inhaled corticosteroids for asthma, especially with beclomethasone and budesonide
- Prolonged use of topical decongestants (> 4 days) can lead to rebound congestion
- Oral decongestants not recommended for children

# 8 Allergic rhinitis referral algorithm

Pharmacy-level referral criteria

Refer your patient to a GP if:

- treatment with an antihistamine and an intranasal corticosteroid (INCS) has not controlled symptoms
- symptom control requires long-term (> 1 month) treatment
- · the patient has comorbidities
- the patient's quality of life is being seriously affected
- there are complications such as pain, anosmia or hearing loss.

#### General-practice-level referral criteria

Refer your patient to an allergy specialist if:

- the patient requests it or wishes to identify triggers or obtain further information on the role of allergy in allergic rhinitis, and the GP considers it appropriate
- the patient has severe allergic comorbidities such as eczema and food allergies, or troublesome or poorly controlled asthma
- complications such as resistant obstruction, anosmia, sinus disease, ear problems, persistent purulent drainage, or behavioural effects are present
- symptoms are persistent and/or severe and/or unresponsive
- expensive or significant life-changing measures (eg, changing address) are being contemplated.

Refer your patient to an ear, nose and throat specialist if:

- the patient has constant unilateral obstruction
- complications such as resistant obstruction, anosmia, sinus disease, ear problems, persistent purulent discharge are present
- a polyp is unresponsive to initial INCS therapy.

on severity of symptoms, failure of previous treatment strategies, the desire to avoid reliance on pharmacotherapy, and presence of comorbid conditions. <sup>18</sup> Box 9 outlines the criteria for selecting candidates for immunotherapy. <sup>36</sup> To avoid serious harm, immunotherapy must be prescribed and administered in accordance with the Australian guidelines for asthma. <sup>36</sup> That is, it should be *prescribed* only by practitioners or teams with appropriate expertise, and administered by clinicians with training and experience in this form of treatment, in a setting with adequate resuscitation facilities and equipment. <sup>36</sup>

#### Conclusion

AR is not a "trivial" or "nuisance" condition; it can have significant detrimental effects on psychological wellbeing and school or work performance. Treatment can provide optimal symptom control and greatly improve quality of life. Moreover, treatment reduces the potential for more severe comorbidity, such as asthma.

Various treatment options are available, from simple strategies for allergen avoidance, to pharmacotherapies (prescription and OTC) and immunotherapy. Treatment choice depends on the individual's symptoms and response to previous therapies. At least two out of three patients with AR select OTC medication (Newspoll Omnibus, 2002. Data on file, GlaxoSmithKline), with INCS the first-line choice.

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## 9 Criteria for immunotherapy in allergic rhinitis\*18,36

#### Indications

- A history indicating that exposure to a particular allergen precipitates symptoms and contributes to illness
- Documented sensitivity to the clinically relevant aeroallergen
- Future exposure to the allergen is unavoidable or only partially reducible
- · An effective allergen extract is available
- Poor response to previous pharmacotherapy for allergic rhinitis

#### Patient-centred factors

- Ability to give informed consent
- Ability to commit to time for immunotherapy

#### Contraindications

- Unstable asthma symptoms
- Concomitant illness immunotherapy is contraindicated in severe pulmonary and cardiovascular disease and should not be initiated in patients with autoimmune disease or malignancy
- Pregnancy initiation of immunotherapy during pregnancy is not recommended because of the risk to the fetus of a systemic 'allergic reaction
- Taking β-blockers
- \* Medical practitioners who administer or supervise allergen immunotherapy must be familiar with the Australian guidelines regarding immunotherapy for asthma, as these guidelines are also applicable to allergic rhinitis. 36

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